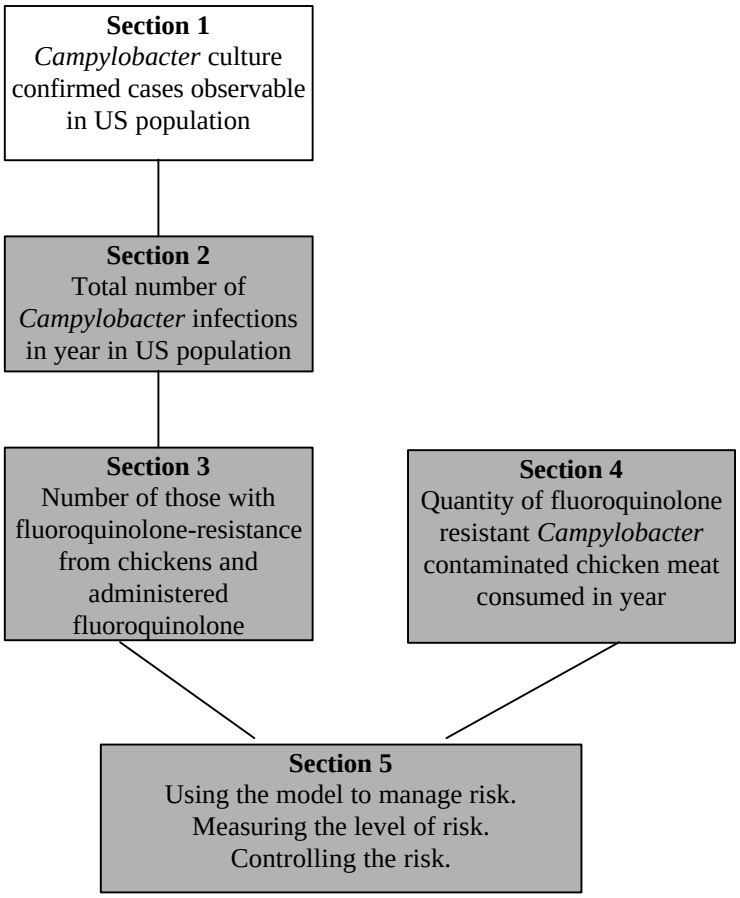
Section 1

Estimating the number of human culture confirmed cases of campylobacteriosis in the U.S. in a specified year



Overview for Sections 1 and 2

The Centers for Disease Control and Prevention (CDC) obtained data for the determination of the annual burden of *Campylobacter* infections through active surveillance, surveys and case control studies. These data sources will be described in detail in Sections 1 and 2. Assumptions made in the risk assessment are presented in the sections adjacent to the data points to which they apply and are listed separately in Appendix C.

Section 1 explains the process of extrapolating the number of culture-confirmed cases reported to the CDC's active surveillance system to the total number of culture-confirmed cases in the U.S. It also details how the total number of culture-confirmed cases is apportioned into confirmed cases of invasive or enteric campylobacteriosis. The enteric cases are further apportioned into those with bloody diarrhea and those without. These three distinct categories of cases, confirmed cases with invasive disease and enteric cases with and without bloody diarrhea, are required in the next step of building the annual number of culture-confirmed *Campylobacter* cases in the U.S.

Section 2 uses the estimated number of culture-confirmed cases in the U.S. calculated in Section 1 to estimate the predicted total number of *Campylobacter* cases in the U.S. Only a small number of cases are reported in FoodNet surveillance, because only a small fraction of persons with campylobacteriosis will progress along the medical care path to the point of becoming a culture-confirmed case. The path includes: seeking health care, having a specimen requested, submitting a specimen when requested to do so, having the laboratory test for *Campylobacter*, and having the laboratory that tests for *Campylobacter* actually finding it. The probabilities of these events occurring differ at points among the three distinct categories listed above.

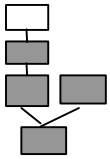
To illustrate the basic steps of the method used to determine the annual burden of *Camplyobacter* infections, the calculations for 1998 are described here using point estimates. The risk analysis calculations of the annual burden of campylobacteriosis are described in Sections 1 and 2 and follow these basic steps but incorporate confidence distributions in place of the point estimates used for demonstration purposes in the pyramids below.

Example – Basic Steps in Calculation of total number of *Campylobacter* infections in the U.S. in 1998

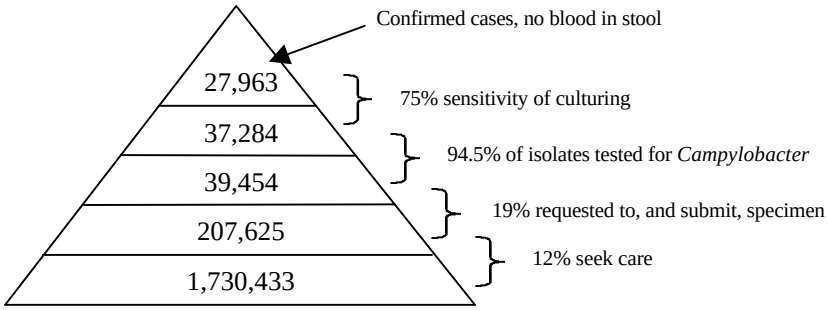
The number of enteric culture-confirmed cases for the U.S. is calculated by multiplying the number of enteric culture-confirmed cases in the FoodNet sites for the year by the ratio of the U.S. population to the FoodNet catchment size. There were 4,028 *Campylobacter* culture-confirmed cases ascertained in FoodNet sites in 1998. Of these cases, 43 were isolated from body sites considered invasive and 3,985 were from stool samples or were of unknown origin. For a national population of 270,298,524 that translates into 51,975 culture-confirmed enteric *Campylobacter* cases. Similarly, there are an estimated 561 culture-confirmed *Campylobacter* cases with invasive disease. Therefore, the total number of culture-confirmed cases, combining those with enteric disease and those with invasive disease, is the sum of these two estimates: 51,975 + 561 or 52,537.

Now 46.2% of those culture confirmed cases in FoodNet in 1998 came from cases with bloody diarrhea (see Section 1.9). This means that 51,976 x 0.462= 24,012 cultures came from cases with bloody diarrhea, and 27,963 cultures came from cases without blood in the stool.

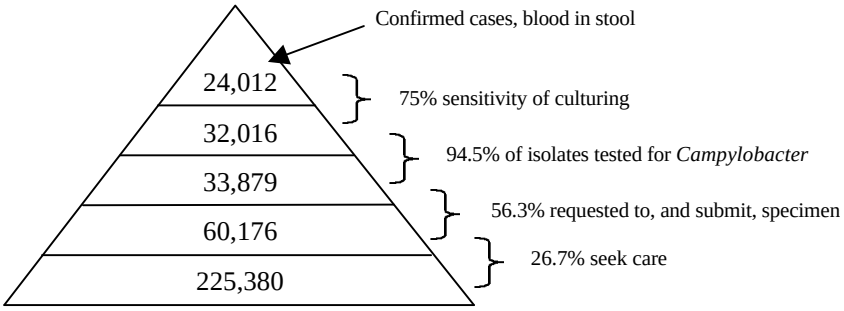
The way the number of culture-confirmed cases is built up to the total number of cases is best illustrated by means of pyramids in the example given below. The values of parameters in the pyramid that apply to cases without bloody diarrhea are different from the values of parameters in the pyramid for cases with bloody diarrhea. The pyramid for *Campylobacter* cases without blood in the stool is as follows:



The calculation begins with the 27,963 predicted confirmed cases in the U.S. That number is divided by 0.75 to adjust for lack of test sensitivity, which are the cases that were tested but failed to yield a positive result. This process of adjustment for the various steps along the medical care path continues down the pyramid until the predicted number of campylobacteriosis cases without blood in the stool in the U.S. is attained at the bottom of the pyramid, 1,730,433 cases.

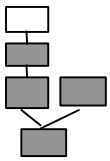


The pyramid for cases with bloody diarrhea contains the assumptions that a larger percentage of persons with bloody diarrhea will seek care, will be requested and will submit specimens when they are requested to do so (Section 2.3).



Finally, the ascertainment rate is assumed to be 100% for cases with invasive campylobacteriosis, obviating the need to use calculations. Thus, the estimated total burden of campylobacteriosis for 1998 is the sum of the three values for cases without bloody diarrhea, with bloody diarrhea, and with invasive disease. That is 1,730,433 + 225,380 + 561 = 1,956,374 cases.

This basic calculation makes use of point estimates derived from CDC data. The remainder of Sections 1 and 2 describe the data points with their inherent uncertainty or confidence distributions that were used in modeling the risk to provide an estimate of the total annual burden of campylobacteriosis.



Symbol	Description	Formula
n_{US}	U.S. population	Data
n_{FN}	FoodNet catchment population	Data
o_i	FoodNet observed invasive cases of Campylobacter	Data
o_e	FoodNet observed enteric cases of Campylobacter	Data
λ_i	Expected observed FoodNet invasive cases of Campylobacter	=Gamma(o_i,1)
λ_e	Expected observed FoodNet enteric cases of Campylobacter	=Gamma(o_e,1)
N_i (= $N1_i$)	Nominal observed mean invasive infections in population	$=\lambda_i * n_{US} / n_{FN}$
N_e	Nominal observed mean enteric infections in population	$=\lambda_e * n_{US} / n_{FN}$
p_b	Proportion of enteric infections with bloody diarrhea	Beta distribution based on data
$N1_{eb}$	Nominal mean number of confirmed enteric infections in population with bloody diarrhea	$=N_e * p_b$
$N1_{en}$	Nominal mean number of confirmed enteric infections in population with non-bloody diarrhea	$=N_e*(1- p_b)$

Parameter estimations

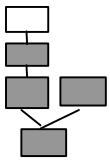
1.1 (n_{us}) – U.S. population (linear extrapolation for 1998)

The numbers used in the calculation of FoodNet incidence rates for the catchment areas and the size of the total U.S. population are obtained from the U.S. Census Bureau post-census estimates, which become available in August each year. These estimates are calculated annually, and for the 1998 post-census estimates were based on 1990 census data. More information about how these population estimates are calculated is available from the U.S. Census Bureau (available at http://www.census.gov/).

For 1998, n_{US} = 270,298,524

1.2 (n_{FN}) - FoodNet Catchment site population

FoodNet is a sentinel surveillance network of Emerging Infections Program Sites. FoodNet was initiated in 1996 in five sites (California, Connecticut, Georgia, Minnesota, Oregon) to provide more accurate national estimates of the burden of foodborne disease than was previously available through passive surveillance (16). By 1998, the FoodNet catchment area had expanded to include the states of Minnesota (MN), Connecticut (CT), Oregon (OR), and selected counties in California (CA), Georgia (GA), Maryland (MD), and New York (NY) (18). The seven sites represented approximately 7.7% (20.5 million) of the U.S. population. Because FoodNet is an active surveillance system, all clinical laboratories within the catchment areas and outside the catchment area, if they receive specimens from persons who reside within the catchment area, are contacted by FoodNet representatives to identify culture-confirmed cases of campylobacteriosis occurring among catchment area residents. Cases are identified from laboratory reports collected for the previous month or are collected more frequently, depending on laboratory volume. Active surveillance is considered more accurate than passive surveillance because it does not rely upon laboratories to provide reports of cases to the surveillance system. Instead, the system contacts and collects the information from the laboratories. FoodNet incidence rates are based upon laboratory-confirmed cases of campylobacteriosis and are being used to document the effectiveness of new food safety control measures. FoodNet incidence rates of culture-confirmed campylobacteriosis therefore include only those persons with campylobacteriosis who sought care for their illness and had a specimen submitted that was tested for and yielded the organism. FoodNet reporting limits case reports to a single report per affected individual within any 12-month period. If more than a single isolation of



Campylobacter from a single individual occurs from multiple specimens, only one, with priority given to the most invasive isolation, is reported to FoodNet for incidence rate estimates.

Culture-confirmed cases of campylobacteriosis represent only a fraction of all *Campylobacter* infections. The majority of persons with *Campylobacter* infections do not seek care and most patients who do seek care are not asked and do not submit specimens for culture (51). The FoodNet data used for 1998 was obtained from preliminary reports and will be updated after publication of the final report.

For 1998, n_{FN} = 20,723,982

1.3 (o_i) - Observed FoodNet invasive cases of *Campylobacter*

Invasive *Campylobacter* infections were ascertained in FoodNet as an isolation of *Campylobacter* from blood, cerebrospinal fluid (CSF), or other normally sterile site. Invasive isolations represent approximately 1.0% of all culture-confirmed *Campylobacter* cases and the vast majority are bloodborne infections (16, 17, 18, 74).

DISCUSSION: It is not precisely known what proportion of persons with invasive *Campylobacter* infections seek care. However, because persons with invasive *Campylobacter* infections will be moderately to severely ill, it is likely that most of these patients will seek care.

Little is known about the completeness of ascertainment of invasive campylobacteriosis. We do not know the frequency with which laboratories are requested to test blood, CSF or other sterile specimens for *Campylobacter*, and we do not know the sensitivity of the diagnostic tests used for isolation from blood and other sterile sites. The lack of this information may result in an underestimate of actual invasive disease rates. However, an increase in isolation of specimens classified as invasive is unlikely to have much impact on the overall number of cases of campylobacteriosis in the U.S. because the currently ascertained proportion of invasive cases is approximately 1.0% of all confirmed cases, and most cases are likely to seek care.

ASSUMPTION: All invasive campylobacteriosis cases seek care, have a specimen collected that yields *Campylobacter*, and is ascertained by FoodNet.

DATA GAP: Data are not available describing rates or cases of invasive disease seeking care, requests for diagnostic tests, and the sensitivity of diagnostic procedures, such as blood culture.

For 1998, o_i = 43

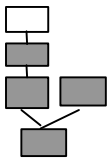
1.4 (o_e) - Observed FoodNet enteric cases of *Campylobacter*

FoodNet reported the number of laboratory-confirmed isolations from stools submitted by persons ill and visiting a health care provider. A FoodNet case is defined as an isolation of *Campylobacter* from a catchment area resident without an isolation in the preceding 12 months.

DISCUSSION: Although the 1998 incidence rates varied by site, from 10.2/100,000 in Maryland to 37.7/100,000 in California from a preliminary FoodNet report (18), the overall rate of *Campylobacter* isolation is likely to reflect isolation rates in the U.S. population. Comparisons of demographic characteristics between the FoodNet sites and the U.S. population show similar distributions of sex, age, race and rural/urban distributions (Table 1.1).

ASSUMPTION: The incidence rates for culture-confirmed *Campylobacter* infections in the FoodNet catchment are representative of incidence rates for culture-confirmed *Campylobacter* infections in the U. S.

For 1998, o_e = 3,985



1.5 (λ_i) and 1.6 (λ_e) - Expected observed FoodNet invasive and enteric cases of *Campylobacter*

The number of invasive and enteric infections in the FoodNet catchment sites that are observed is affected by random chance. The true measure of the health burden is the mean number of observations we would see if we were able to repeat each year many times. The confirmed cases of *Campylobacter* are rare events when compared to the population size, so it is reasonable to assume that the frequency of confirmed cases is a Poisson process. In this case, the mean number of observations are the Poisson means l_i and l_e for invasive and enteric infections respectively. The uncertainty about these means is then modeled using Gamma distributions (see Appendix A), to give:

l_i = Gamma(o_i,1)
l_e = Gamma(o_e,1)

which give the following distributions:

l_i	l_e
Gamma(43,1)	Gamma(3 985,1)

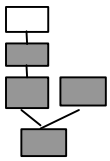
Figure A5a shows the Gamma(43,1) distribution for the 1998 estimate of l_i. The distribution is centered around the observed value of 43, but because this is a small number the distribution extends over a range between 25 and 70. In other words, we are recognizing that although we observed 43 cases in 1998, we may have an average number of cases for the year anywhere between 25 and 70 if we were able to repeat the year again and again. Figure A5b shows the Gamma(3 985,1) distribution for the 1998 estimate of l_e. This distribution is proportionally far narrower than that for l_i because there are many more observations. Therefore, we are relatively more confident of the true value.

1.7 (N_i) and 1.8 (N_e) - Nominal observed mean invasive and enteric infections in population

The FoodNet sites cover only (n_{FN} / n_{US}) of the population, so estimates of the mean number of cases that would apply to the population are calculated by dividing l_i and l_e by this fraction. This extrapolation from FoodNet catchment populations to the U.S. population at large assumes that the FoodNet catchment populations will, in aggregate, be reasonably representative of the U.S. population (Table 1.1).

$N_i = \lambda_i * n_{US}/n_{FN}$
$N_e = \lambda_e * n_{US}/n_{FN}$

Sentinel surveillance systems provide incidence estimates for the catchment area being monitored, and are not necessarily representative of the U.S. population. Incidence rates from sentinel surveillance systems are intended to be indicative of, but not necessarily the same as, disease rates in other parts of the country. A comparison of demographic statistics between the FoodNet catchment population and the U.S. population was made because the extrapolation of rates observed in the FoodNet catchment area to an estimate of the burden of disease in the U.S. population was necessary for the risk assessment, (Table 1.1). Comparing FoodNet and U.S. populations by demographic characteristics (sex, age, race, and rural-to-urban distribution), the population distributions appear to be similar. The exception may be the lower proportion of Hispanics represented in FoodNet catchment areas compared to the U.S. population. The demographic characteristics available for comparison are, in most instances, only markers for other risk factors that influence the rates of disease in populations. The ideal extrapolation of FoodNet incidence rates to the U.S. population would require knowledge of the distribution of risk factors that affect the rates of disease. However, many of these risk factors are not well described. Some risk factors for



campylobacteriosis are age (the most susceptible are the very young and elderly), immune status (the immunocompromised are most at risk), and antibiotic therapy in the month prior to illness onset (74). Because the comparison of demographic characteristics between the FoodNet and the U.S. populations was similar, this indicates that the risk factors that affect disease rates may also be distributed similarly. Therefore, the rates of disease obtained from FoodNet are likely to be representative of disease rates in the U.S.

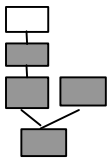
Table 1.1. Comparison of the Distribution of Demographic Characteristics by FoodNet Total Catchment to U.S. Population

Demographic Characteristic		FoodNet Total Catchment Area	U.S. Population
Rural vs. Urban[1]	Rural	4,076,398 (21.78)	61,656,386 (24.80)
	Urban	14,637,400 (78.22)	187,053,487 (75.20)
Age Distribution	0-<1 year	280,015 (1.35)	3,776,389 (1.40)
	1-<10 years	2,907,058 (14.03)	39,050,749 (14.45)
	10-<20 years	2,865,920 (13.83)	38,050,749 (14.29)
	20-<30 years	2,767,848 (13.36)	36,296,139 (13.43)
	30-<40 years	3,591,391 (17.33)	43,608,568 (16.13)
	40-<50 years	3,201,640 (15.45)	39,778,258 (14.72)
	50-<60 years	2,047,441 (9.88)	26,692,895 (9.88)
	60+ years	3,062,669 (14.78)	42,472,248 (15.71)
Sex	Male	10,148,135 (48.97)	132,046,334 (48.85)
	Female	10,575,847 (51.03)	138,252,190 (51.03)
Race	Native American	126,418 (0.61)	2,000,000 (0.74)
	White	15,913,196 (76.79)	195,439,508 (72.31)
	Black	2,534,928 (12.23)	32,717,955 (12.10)
	Hispanic	1,147,715 (5.54)	30,250,255 (11.19)
	Asian	1,001,725 (4.83)	9,890,223 (3.66)

[1]1990 U.S. Census Estimates

In addition to demonstrating similarity in population composition, an evaluation of potential exposure is important. Human exposure to *Campylobacter* is based upon prevalence of *Campylobacter* on chicken and the proportion of the population exposed to chicken. In a 1994-5 United States Department of Agriculture, Food Safety Inspection Service, survey, 88% of chicken carcasses were reported to carry *Campylobacter* at slaughter (Table 1.2)(81). Another estimate, of retail chicken product Campylobacter carriage was demonstrated at a level of 88% in a Minnesota survey of chicken products in 1997 (71).

Sporadic cases of *Campylobacter* account for approximately 99% of all *Campylobacter* cases. Epidemiologic investigations of sporadic infections have indicated that chicken is the most common source of human infections (2, 71, 74). The frequency of chicken consumption was evaluated to assess exposure to this risk factor in the U.S. population. The National Chicken Council provided a chicken consumption survey, conducted by Bruskin Goldring Research in June 1999 (15). The survey utilized computer-assisted telephone interviewing and evaluated the frequency of chicken consumption at home or away from home by sex, age, income and region. The sample consisted of 1,019 completed interviews of males and females, at least 18 years of age, in approximately equal numbers. The selection of interviewees was based upon a computer-based random-digit dialing sample of all households with telephones in the continental U.S. There was equal probability of selection for each household with a telephone, including listed and unlisted numbers. Each number was subject to an original and at least four follow-up attempts to complete the interviews. Findings, at a 5% level of confidence, indicated that there was no difference in frequency of chicken consumption at home or away from home by sex. Frequency of chicken consumption at home or away from home was slightly greater for younger respondents 18-24 years of age (mean=8.3 times per month, $p<0.05$) compared to other age groups (range of means=6.6-7.6 times per month,



p<0.05). Respondents from the Northeast (mean=8.2 times per month, p<0.05), consumed chicken at home more frequently compared to other parts of the country (range of means=6.1-7.5 times per month, p<0.05), but when eating chicken away from home all regions were similar. The proportion of people rarely or never consuming chicken was low and did not vary significantly by sex, age, income or region of the U.S. at a 95% confidence level (15).

Table 1.2. Percent Isolation of *Campylobacter* and Level of Contamination

Food Animal	Source	No. Sampled	Percent Positive	Concentration[1] MPN/cm^2	Year	Ref
Cattle						
Slaughterhouse	Carcass (Strs[2] & Heifers)	2064	4	0.1 (CI NA)[3]	1992-3	83
Slaughterhouse	Carcass (Cows & Bulls)	2109	10	0.1 (CI 0.1- 0.2)	1993-4	82
Slaughterhouse	Ground Beef[4]	562	0	NA	1993-4	84
Swine						
Slaughterhouse	Carcasses	2,112	32	0.1 (CI 0.08-0.13)	1995-6	85
Broiler Chickens						
Slaughterhouse	Carcasses	1297	88	4.4 (CI 3.8-5.1)	1994-5	81
Processing Plant	Grd. Chicken[5]	283	60	4.8 (CI 4.0-5.7)	1995	86
Turkeys						
Slaughterhouse	Carcasses	1221	90	0.18 (CI 0.16-0.20)	1996-7	69
Slaughterhouse	Ground Turkey[6]	295	25	2.8 (CI 0.42-18.52)	1995	87

[1]MPN-Most Probable Number indicates most likely level of contamination, not actual level because enrichment steps were required to isolate *Campylobacter*. Carcass units are MPN/cm^2 and ground product units are MPN/g.
[2] Strs=Steers, CI- 95% Confidence Interval
[3] Not applicable
[4] Sampling period omitted sampling between March through August
[5] Grd=Ground, Sampling period omitted collection between June through September.
[6]Sampling period omitted collection between March through and September.

1.9 (p_b) - Proportion of culture confirmed enteric infections with bloody diarrhea

The estimation of this parameter used two sources of data. The proportion of culture-confirmed enteric infections with patients reporting bloody diarrhea was calculated from the *Campylobacter* Case Control study for each FoodNet site (CA=18.2% (2/11), CT=40.2% (70/174), GA=53.6% (15/28), MD=47.6% (10/21), MN=49.1% (113/230), NY=50.8% (32/63), OR=54.6% (6/11) and weighted by catchment site population (18). The estimate weighted by catchment population was 46.2%, and the crude estimate was 46.1%. See Table 1.3.

A second estimate from a survey of eight sites participating in the National Nosocomial Infections Study was also used. Of culture-confirmed cases of campylobacteriosis with diarrhea as a symptom collected between Jan. 1, 1980, and Mar. 31, 1981, 46% (101/220) reported observable blood in their stools (14).

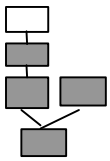


Table 1.3. Catchment Populations and Cases Reporting to Have Had Blood in Their Stools. (*Campylobacte*r Case Control Study)

Site j	Catchment population	Weighting Fraction W_j	Number for whom response was known A_j	Number who had bloody diarrhea B_j
CA	2,146,096	0.103556	11	2
CT	3,274,069	0.157985	174	70
GA	3,746,059	0.18076	28	15
MD	2,444,280	0.117945	21	10
MN	4,725,419	0.228017	230	113
NY	1,106,085	0.053372	63	32
OR	3,281,974	0.158366	11	6
Total	20,723,982	1	538	248

The FoodNet data for reporting blood in the stool was used as follows to determine an estimate for p_b:

$$p_b = \sum_j W_j * Beta(B_j + 1, A_j - B_j + 1)$$

where W_j is the weight for site j (site j size over total catchment size), B_j is the site-specific number of cases reporting bloody diarrhea and A_j is the site-specific number of cases providing a response to whether blood had been observed in their stools. The Beta distribution is used here to describe the uncertainty about a proportion, as explained in Appendix A. Each of the summed Beta distributions is approximately normally distributed because there are reasonably large samples (D_j) and because the Beta distributions are centered at values near 0.5 (i.e. B_j/A_j are approximately 0.5). The distribution of p_b can thus be approximated by first replacing each Beta distribution with a Normal:

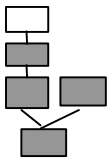
$$Beta(B_j + 1, A_j - B_j + 1) \approx Normal(m_j, s_j)$$

where

$$m_j = \frac{B_j + 1}{A_j + 2} \text{ and } s_j = \sqrt{\frac{(B_j + 1)(A_j - B_j + 1)}{(A_j + 2)^2 (A_j + 3)}}$$

and then noting the identity:

$$p_b \approx \sum_j W_j * Normal(m_j, s_j) = Normal\left(\sum_j W_j m_j, \sqrt{\sum_j (W_j s_j)^2} \right)$$



This can then be converted back to a Beta distribution using the formulae (42):

$$p_b = Beta(a_1, a_2)$$

where

$$a_1 = \frac{m^2(1-m)}{s^2} - m$$

$$a_1 + a_2 = \frac{m(1-m)}{s^2} - 1$$

and

$$m = \sum_j W_j m_j,$$

$$s = \sqrt{\sum_j \left(W_j s_j\right)^2}$$

The National Nosocomial Infections Study data showed that of 220 culture-confirmed cases, 101 had reported observable blood in their diarrhea. We can use this data to update the estimate of p_b from Beta (a_1, a_2) as follows (See Appendix A for details):

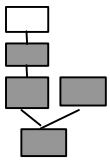
p_b = Beta(a_1 + 101, a_2 + 220-101)

1.10 ($N1_{en}$, $N1_{eb,}$ $N1_i$) - Nominal mean number of culture confirmed enteric infections in population with self reported bloody and non-bloody diarrhea and the nominal mean number of culture confirmed invasive infections in the population

These enteric infection parameters are calculated by multiplying the nominal observed mean enteric infections in the population by the probabilities a case will report visible blood in the diarrhea p_b and (1-p_b) the probability of reporting no visible blood in the diarrhea respectively. The number of invasive cases is not subdivided, thus:

$N1_{eb} = N_e * p_b$
$N1_{en} = N_e*(1- p_b)$
$N1_i = N_i$

In mathematical terms, $N1_{eb}$ and $N1_{en}$ are the mean values (intensities) of Poisson distributions and p_b has been interpreted as the probability that an individual contracting campylobacteriosis will report visibly bloody stools. An alternative interpretation of p_b would be the predictably constant fraction of the population contracting campylobacteriosis that would report visibly bloody stools because of some mechanism. The approach used in this model allows for greater variability in the observable incidence of bloody diarrhea and, therefore, produces greater uncertainty in our estimates of the mean incidence.



Section 1 Summary

The model predicts that in 1998 there were about 28,077 [90% confidence interval is (27,339, 28,801)] confirmed (i.e. identified by a healthcare provider) cases of campylobacteriosis with non-bloody diarrhea, 23,898 [90% confidence interval is (23,289, 24,534)] confirmed cases with bloody diarrhea, and 561 [90% confidence interval is (428, 708)] confirmed invasive disease cases. Relative contributions of the various components of the model to the total model uncertainty will be presented in Section 5, Sensitivity Analysis.